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Protexeon Limited
Aldwych House
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London
WC2B 4HN

Patents ADP number *(if you know it)* — 8375784001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — USE

5. Name of your agent *(if you have one)* — D Young & Co

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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EC4A 1DA

Patents ADP number *(if you know it)* — 59006

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — Yes

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9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	-
Description	16
Claim(s)	3 DL
Abstract	1
Drawing(s)	7 + 7

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11. I/We request the grant of a patent on the basis of this application.

Signature(s) D Young & Co

Date 10 October 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

D Young & Co (Agents for the Applicants)

Zöe Clyde-Watson 020 7353 4343

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USE

The present invention relates to a method of treating neonatal asphyxia.

BACKGROUND TO THE INVENTION

Neonatal (or perinatal) asphyxia, also known as hypoxia-ischemia, is a condition arising from the inadequate intake of oxygen in an infant during labour, delivery, or the immediate postnatal period. Neonatal asphyxia is an important cause of morbidity and mortality in the newborn and commonly leads to hypoxic-ischemic encephalopathy.

Studies have shown that neonatal asphyxia (hypoxia) for as short a time as six minutes can lead to permanent neurological damage. Loss of brain tissue has been demonstrated in asphyxiated newborn primates and correlated with memory dysfunction and spastic paralysis [Windle, WF. Brain Damage by Asphyxia at Birth. Scientific American 1969 Oct; 221(4):76-84].

About 14.6% of all deaths at birth are caused by neonatal asphyxia. In the western world about 0.9% (i.e. 100-130,000) of newborns suffer from neonatal asphyxia. About 10% die and another 15% are severely handicapped due to long-term complications such as mental retardation, spasticity, learning difficulties and/or epilepsy. Furthermore, it is increasingly recognized that children with rather mild asphyxia, who seem initially to recover without complications, have behavioral problems in childhood, which can be traced back to this neonatal insult. Neonatal asphyxia meets the criteria for an orphan drug indication since it affects less then 5 patients in 10,000 inhabitants, and is a life-threatening, serious debilitating disease without an established therapy.

The present invention seeks to provide a method of treating neonatal asphyxia.

STATEMENT OF INVENTION

A first aspect of the invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said medicament is for use in combination with hypothermia.

A second aspect of the invention relates to a method of treating neonatal asphyxia in a mammal in need thereof, said method comprising:

(a) administering a therapeutically effective amount of xenon to the mammal; and

(b) subjecting the mammal to hypothermia.

A third aspect of the invention relates to a method of treating neonatal asphyxia in a mammal in need thereof, said method comprising administering a therapeutically effective amount of xenon to the mammal in combination with hypothermia.

A fourth aspect of the invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said treatment comprises administering to a subject simultaneously, sequentially or separately xenon in combination with hypothermia.

A fifth aspect of the invention relates to the use of xenon, in combination with hypothermia, for the treatment of neonatal asphyxia.

DETAILED DESCRIPTION

As mentioned above, a first aspect of the present invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said medicament is for use in combination with hypothermia.

As used herein, the term "hypothermia" refers to subjecting a particular subject (in this case, a neonatal subject) to hypothermic conditions, for example, by lowering the body temperature, preferably by 3-5°C, through passive or active techniques. Typically, subjecting to hypothermic conditions leads to a decrease in metabolism of body tissues of the subject, thereby decreasing the need for oxygen.

The use of hypothermia in the treatment of neonatal asphyxia is well documented in the art [see for example, Volpe, Mental Retardation and Developmental Disabilities Research Reviews 2001, 7: 56-64; Gunn *et al* Curr Opin Pediatr. 2000 Apr;12(2):111-5]. However, to date there has been no teaching or suggestion in the art that hypothermia could be use in combination with the administration of xenon. Nor has there been any suggestion that such combination therapy would lead to such a surprising and unexpected enhancement in the resulting neuroprotective effect.

Xenon is a chemically inert gas whose anaesthetic properties have been known for over 50 years [Lawrence JH *et al*, J. Physiol. 1946; 105:197-204]. Since its first use in surgery [Cullen SC *et al*, Science 1951; 113:580-582], a number of research groups have shown it has an excellent pharmacological profile, including the absence of metabolic by-products, profound analgesia, rapid onset and recovery, and minimal effects on the cardiovascular system [Lachmann B *et al*, Lancet 1990; 335:1413-1415; Kennedy RR *et al*, Anaesth. Intens. Care 1992; 20:66-70; Luttropp HH *et al*, Acta Anaesthesiol. Scand. 1994; 38:121-125; Goto T *et al*, Anesthesiology 1997; 86:1273-1278; Marx T *et al*, Br. J. Anaesth. 1997; 78:326-327].

It has recently been discovered that xenon (which rapidly equilibrates with the brain) is an NMDA antagonist [Franks NP *et al*, Nature 1998; 396:324]. Mechanistic studies on cultured hippocampal neurons have shown that 80% xenon, which will maintain surgical anaesthesia, reduces NMDA-activated currents by up to 60%. This powerful inhibition of the NMDA receptor explains some of the important features of the pharmacological profile and is likely to be instrumental in the anaesthetic and analgesic effects of this inert gas.

Previous studies by the applicant have revealed that xenon has neuroprotective properties. In particular, WO 01/08692, the contents of which are incorporated herein by reference, relates to the use of xenon as a neuroprotectant and/or as an inhibitor of synaptic plasticity. However, there is no teaching or suggestion in the prior art that xenon would be effective as a neuroprotectant in the context of the presently claimed invention.

As used herein, the term "neuroprotectant" means an agent that is capable of providing neuroprotection, i.e., protecting a neural entity, such as a neuron, at a site of injury, for example, an ischaemic injury or traumatic injury.

In a preferred embodiment, the xenon is an NMDA antagonist.

The term "antagonist" is used in its normal sense in the art, i.e., a chemical compound which prevents functional activation of a receptor by its natural agonist (glutamate, in this case).

The NMDA (N-methyl-D-aspartate) receptor is a major subclass of glutamate receptor and glutamate is believed to be the most important excitatory neurotransmitter in the mammalian central nervous system. Importantly, activation of the NMDA receptor has been shown to be the central event which leads to excitotoxicity and neuronal death in many disease states, as well as a result of hypoxia and ischaemia following head trauma, stroke and following cardiac arrest.

It is known in the art that the NMDA receptor plays a major role in the synaptic plasticity which underlies many higher cognitive functions, such as memory and learning, as well as in certain nociceptive pathways and in the perception of pain (Collingridge *et al*, The NMDA Receptor, Oxford University Press, 1994). In addition, certain properties of NMDA receptors suggest that they may be involved in the information-processing in the brain which underlies consciousness itself.

NMDA receptor antagonists are therapeutically valuable for a number of reasons. Firstly, NMDA receptor antagonists confer profound analgesia, a highly desirable component of general anaesthesia and sedation. Secondly, NMDA receptor antagonists are neuroprotective under many clinically relevant circumstances (including ischemia, brain trauma, neuropathic pain states, and certain types of convulsions). Thirdly, NMDA receptor antagonists confer a valuable degree of amnesia.

However, there are a number of drawbacks associated with many conventional NMDA receptor antagonists. These include the production of involuntary movements, stimulation of the sympathetic nervous system, induction of neurotoxicity at high doses (which is pertinent since NMDA receptor antagonists have low potencies as general anaesthetics), depression of the myocardium, and proconvulsions in some epileptogenic paradigms e.g., "kindling" (Wlaz P *et al*, Eur. J. Neurosci. 1994; 6:1710-1719). In particular, there have been considerable difficulties in developing new NMDA receptor antagonists that are able to cross the blood-brain barrier. This factor has also limited the therapeutic applications of many known NMDA antagonists.

Unlike many other NMDA antagonists, xenon is able to rapidly equilibrate with the brain by diffusing across the blood brain barrier. A further advantage of using xenon as an NMDA antagonist is that the molecule is an inert, volatile gas that can be rapidly eliminated via respiration.

In one preferred embodiment of the invention, the xenon is admixed with a pharmaceutically acceptable diluent, excipient or carrier.

Examples of such suitable excipients for the various different forms of pharmaceutical compositions described herein may be found in the "Handbook of Pharmaceutical Excipients, 2nd Edition, (1994), Edited by A Wade and PJ Weller.

Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). Examples of suitable carriers include lactose, starch, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol and the like. Examples of suitable diluents include ethanol, glycerol and water.

The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as, or in addition to, the carrier, excipient

or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s).

Examples of suitable binders include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, corn sweeteners, natural and synthetic gums, such as acacia, tragacanth or sodium alginate, carboxymethyl cellulose and polyethylene glycol.

Examples of suitable lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

Preservatives, stabilizers and dyes may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

The present invention is also applicable to the treatment of animals. In this regard, the invention further relates to the use of xenon in combination with a veterinarily acceptable diluent, excipient or carrier.

For veterinary use, the xenon is typically administered in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

The xenon may also be administered in combination with another pharmaceutically active agent. The agent may be any suitable pharmaceutically active agent including anaesthetic or sedative agents which promote GABAergic activity. Examples of such GABAergic agents include isoflurane, propofol and benzodiazapines.

The xenon may also be administered in combination with other active ingredients such as L-type calcium channel blockers, N-type calcium channel blockers, substance P antagonists, sodium channel blockers, purinergic receptor blockers, or combinations thereof.

The xenon may be administered by any suitable delivery mechanism, or two or more suitable delivery mechanisms.

In one particularly preferred embodiment, the xenon is administered by perfusion. In the context of the present invention, the term "perfusion" refers to the introduction of an oxygen/xenon mixture into, and the removal of carbon dioxide from, a patient using a specialised heart-lung machine. In general terms, the heart-lung machine replaces the function of the heart and lungs and provides a bloodless, motionless surgical field for the surgeon. The perfusionist ventilates the patient's blood to control the level of oxygen and carbon dioxide. In the context of the present invention, the perfusionist also introduces xenon into the patient's blood. The perfusionist then propels the blood back into the arterial system to provide nutrient blood flow to all the patient's vital organs and tissues during surgery.

In one particularly preferred embodiment, the medicament is in gaseous form.

In another highly preferred embodiment, the xenon is administered by inhalation. More preferably, the xenon is administered by inhalation of a 70-30% v/v xenon/oxygen mixture.

More preferably, the xenon is administered in the form of a 20-70% v/v xenon/air mixture.

In yet another preferred embodiment of the invention, the medicament is in the form of a liquid or solution.

Preferably, the liquid is administered in the form of a solution or an emulsion prepared from sterile or sterilisable solutions, which may be injected intravenously, intraarterially, intrathecally, subcutaneously, intradermally, intraperitoneally or intramuscularly.

In one particularly preferred embodiment, the xenon is administered in the form of a lipid emulsion. The intravenous formulation typically contains a lipid emulsion (such as the commercially available Intralipid®10, Intralipid®20, Intrafat®, Lipofundin®S or Liposyn® emulsions, or one specially formulated to maximise solubility) which sufficiently increases the solubility of the xenon to achieve the desired clinical effect. Further information on lipid emulsions of this sort may be found in G. Kleinberger and H. Pamperl, Infusionstherapie, 108-117 (1983) 3.

The lipid phase of the present invention which dissolves or disperses the gas is typically formed from saturated and unsaturated long and medium chain fatty acid esters containing 8 to 30 carbon atoms. These lipids form liposomes in aqueous solution. Examples include fish oil, and plant oils such as soya bean oil, thistle oil or cottonseed oil. The lipid emulsions of the invention are typically oil-in-water emulsions wherein the proportion of fat in the emulsion is conventionally 5 to 30% by weight, and preferably 10 to 20% by weight. Oil-in-water emulsions of this sort are often prepared in the presence of an emulsifying agent such as a soya phosphatide.

The lipids which form the liposomes of the present invention may be natural or synthetic and include cholesterol, glycolipids, sphingomyelin, glucolipids, glycosphingolipids, phosphatidylcholine, phosphatidylethanolamine, phosphatidyl-serine, phosphatidyglycerol, phosphatidylinositol.

The lipid emulsions of the present invention may also comprise additional components. These may include antioxidants, additives which make the osmolarity of the aqueous phase surrounding the lipid phase isotonic with the blood, or polymers which modify the surface of the liposomes.

It has been established that appreciable amounts of xenon maybe added to a lipid emulsion. Even by the simplest means, at 20°C and normal pressure, xenon can be dissolved or dispersed in concentrations of 0.2 to 10 ml or more per ml of emulsion. The concentration of dissolved gas is dependent on a number of factors, including temperature, pressure and the concentration of lipid.

The lipid emulsions of the present invention may be loaded with gaseous xenon. In general, a device is filled with the emulsion and anaesthetics as gases or vapours passed through sintered glass bubblers immersed in the emulsion. The emulsion is allowed to equilibrate with the anaesthetic gas or vapour at a chosen partial pressure. When stored in gas tight containers, these lipid emulsions show sufficient stability for the anaesthetic not to be released as a gas over conventional storage periods.

The lipid emulsions of the present invention may be loaded so that the xenon is at the saturation level. Alternatively, the xenon may be present in lower concentrations, provided, for example, that the administration of the emulsion produces the desired pharmaceutical activity.

The concentration of xenon employed in the invention may be the minimum concentration required to achieve the desired clinical effect. It is usual for a physician to determine the actual dosage that will be most suitable for an individual patient, and this dose will vary with the age, weight and response of the particular patient. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Preferably, the medicament is in a form suitable for intravenous, neuraxial or transdermal delivery.

Preferably, the xenon is administered simultaneously, in combination, sequentially or separately with hypothermia..

As used herein, "simultaneously" is used to mean that the xenon is administered concurrently with hypothermia, whereas the term "in combination" is used to mean the xenon is administered, if not simultaneously, then "sequentially" within a timeframe in which the xenon and the hypothermia both exhibit a therapeutic effect, i.e. they are both are available to act therapeutically within the same time-frame. Thus, administration "sequentially" may permit the xenon to be administered within 5 minutes, 10 minutes or a matter of hours before the hypothermia, provided the

circulatory half-life of the xenon is such that it is present in a therapeutically effective amount when the neonatal subject is exposed to hypothermic conditions.

In contrast to "in combination" or "sequentially", "separately" is used herein to mean that the gap between administering the xenon and exposing the neonatal subject to hypothermia is significant i.e. the xenon may no longer be present in the bloodstream in a therapeutically effective amount when the neonatal subject is exposed to hypothermic conditions.

More preferably, the xenon is administered sequentially or simultaneously with hypothermia, more preferably simultaneously.

In one preferred embodiment of the invention, the xenon is administered in a therapeutically effective amount.

In another preferred embodiment, the xenon is administered in a sub-therapeutically effective amount. In other words, the xenon is administered in an amount that would be insufficient to produce the desired therapeutic effect if administered in the absence of hypothermic conditions.

Even more preferably, the combination of xenon and hypothermia has a synergistic effect, i.e., the combination is synergistic.

Preferably, the hypothermia is maintained for a period of at least about 6 hours, more preferably at least about 12 hours, after the hypoxic-ischemic (HI) insult.

In one preferred embodiment, the hypothermia is maintained for a period of from about 6 to about 24 hours after the hypoxic-ischemic (HI) insult.

Preferably, the hypothermia is maintained for a period of at least about 6 hours, more preferably at least about 12 hours, after birth.

In one preferred embodiment, the hypothermia is maintained for a period of from about 6 to about 24 hours after birth.

Preferably, treatment in accordance with the method of the invention is initiated within about 6 hours of the hypoxic-ischemic (HI) insult, and more preferably within about 2 hours of the hypoxic-ischemic insult.

Hypothermia may be produced passively, by allowing the temperature to drift downwards and not purposefully sustain body temperature. Being poikilothermic, neonates rapidly assume the temperature of their surroundings. Alternatively the patient may be actively rendered hypothermic by deliberately reducing their ambient temperature.

A second aspect of the invention relates to a method of treating neonatal asphyxia in a mammal in need thereof, said method comprising:

(a) administering a therapeutically effective amount of xenon to the mammal; and

(b) subjecting the mammal to hypothermia, or hypothermic conditions.

In a preferred embodiment, the mammal is a newborn subject in the first four weeks after birth. More preferably, the mammal is in the first two weeks, more preferably still, the first week after birth.

Preferably, the mammal is a human.

Preferably, the mammal is subjected to conditions of mild hypothermia. As used herein, the term "mild hypothermia" typically refers to a decrease in the core temperature from 37°C to about 33°C

In one preferred embodiment, the temperature of the mammal is maintained at a temperature of from about 31°C to about 36°C.

More preferably, the temperature of the mammal is maintained at a temperature of from about 32 °C to about 36 °C, more preferably from about 32 °C to about 35 °C, more preferably still from about 33 °C to about 35 °C.

Preferred embodiments for the second aspect of the invention are the same as those described above in respect of the first aspect.

Another aspect of the invention relates to a method of treating neonatal asphyxia in a mammal in need thereof, said method comprising administering a therapeutically effective amount of xenon to the mammal in combination with hypothermia.

Yet another aspect of the invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said treatment comprises administering to a subject simultaneously, sequentially or separately xenon in combination with hypothermia.

A further aspect of the invention relates to the use of xenon, in combination with hypothermia, for the treatment of neonatal asphyxia.

The present invention is further described by way of example, and with reference to the following figures, wherein:

Figure 1 shows the relationship between damage, as measured by loss of brain weight (ratio of right hemisphere/left) and the duration of the hypoxic period (in minutes) in Sprague-Dawley rats.

Figure 2 shows brain sections from Sprague-Dawley rats that have suffered 90 minutes of hypoxia-ischemia injury.

Figure 3 shows the major cellular damage which is evident in Sprague-Dawley rats 24 hours after 90 minutes of hypoxia-ischemia.

Figure 4 shows the concentration-dependence of xenon neuroprotection (ratio right hemisphere weight/left against xenon concentration).

Figure 5 shows the effect of 70% xenon on neurological functions assessed remotely after hypoxic-ischemic (HI) insult.

Figure 6 compares the neuroprotective effect (ratio of right hemisphere/left) observed with with N_2 and xenon respectively, when xenon is administered 2 hours post HI insult.

Figure 7 shows the effect of mild hypothermia on the neuroprotective effect of xenon (LDH release against xenon concentration, % atm).

Figure 8 shows a van't Hoff plot of the natural logarithm of LDH release plotted against reciprocal absolute temperature.

A more detailed discussion of these figures may be found in the following Examples section.

EXAMPLES

Neonatal Asphyxia Model

Seven day old postnatal Sprague-Dawley rats underwent right common carotid artery ligation under surgical anaesthesia (1%-1.5% isoflurane in pure oxygen). After ligation, the animals were returned to their mothers and placed in a specially designed area with constant of room temperature (23°C) and humidity (48%). One hour after surgery, neonatal rats were placed in specially designed chamber with 8% oxygen combined with 0, 20, 40, 60 or 70% Xenon (with nitrogen making up the balance) for 90 min at 37°C (temperature kept by water bath running outside chambers). At post-experimental day 7, rats (14 day old) were killed and their brains removed. The ratio of right hemisphere weight against left (R/L ratio) was calculated. Rat pups in some groups were allowed to live up to 30 days of postnatal age, at which time their neuromotor

function and co-ordination were assessed with established protocols (Neuromotor testing and Rotarod testing).

The results indicate that with increasing times of hypoxia, damage (as measured by loss of brain weight) is only evident when the hypoxia exceeds 90 minutes (Figure 1). Hence, the standard period of hypoxic injury was set to be 90 minutes.

Brain sections from animals that suffered 90 minutes of hypoxia-ischemia injury are shown in Figure 2. In more detail, Figure 2 (centre) show gross anatomical deterioration (on the side of the brain that sustained the injury - left side in this view) compared to control animals (left). The brain slices on the right are from animals that have suffered the same hypoxia-ischemia but have been breathing 70% xenon during the hypoxic period. These brains look close to normal showing the remarkable neuroprotection afforded by xenon.

The major cellular damage which is evident 24 hours after 90 minutes of hypoxia-ischemia is shown in Figure 3.

The concentration-dependence of xenon neuroprotection (ratio right hemisphere weight/left against xenon concentration) is shown in Figure 4. In more detail, Figure 4 shows the ratios of ipsilateral/contralateral hemispheric weight of 14 day rat brain after hypoxia/ischemia with or without various concentrations of xenon at 7 days old. Neuroprotection is evident even at sub-anaesthetic concentrations. Control animals were subjected to carotid ligation but no hypoxia was given. Results are mean ± SEM ($n = 5 - 8$). * $P < 0.01$ *vs* 8% O_2.

The effect of 70% xenon on neurological functions assessed remotely after hypoxic-ischemic (HI) insult is shown in Figure 5. At postnatal day 7 the right carotid artery was ligated and rat pups were exposed to a hypoxic environment (8% oxygen + 70% xe and balance with nitrogen) for 90 min. Thirty days after the insult, rats were evaluated for neuromotor function (A) using a panel that included assays of prehensile traction, strength, and balance beam performance (graded on a 0-9 scale) and (B) balance on a

Rotarod, a standard test of balance and neuromotor function. The data point from an individual rat is the sum of three tests. The horizontal bars indicate the median for each group.

The neuroprotective effect (ratio of right hemisphere/left) observed with with N_2 and xenon respectively is shown in Figure 6, when xenon is admin istered 2 hours post HI insult. In more detail, the data show that xenon is effective in providing neuroprotection even if it is administered 2 hours after the end of the hypoxic period. The ratios of ipsilateral/contralateral hemispheric weight of 14 day rat brain after 90 min hypoxic-ischemia insult and then 2 hrs recovery following exposure with 70%N_2 or 70% Xe + 30% O_2 for 90 min at 7 days old. Results are mean ± SEM (n = 6).

The effect of mild hypothermia on the neuroprotective effect of xenon (LDH release against xenon concentration, % atm) is shown in Figure 7. Modest hypothermia produces a very large and unexpected enhancement in xenon neuroprotection. Cooling by 4 degrees greatly enhances the potency of xenon in blocking LDH release. In more detail, this figure shows the effect of a combination of xenon and hypothermia on oxygen-glucose deprivation (OGD)-induced lactate dehydrogenase (LDH) release. Figure 7 shows the results of exposing neuronal cultures to 75 minutes OGD in the presence of increasing concentrations of xenon, either at 37°C (red), or at 33°C (blue). The ED_{50} values for xenon at 37°C vs xenon at 33°C were 35.9 +/- 2.15% and 11.5 +/- 2.0% (means +/- SEM) respectively. Neuronal injury is expressed as a percentage of the maximal LDH release after 75 minutes of OGD and 6 hours of recovery in the absence of either xenon or hypothermia. Points represent mean values, with error bars indicating standard errors.

The extent of the temperature-dependence of the process is shown in Figure 8 which shows a van't Hoff plot of the natural logarithm of LDH release plotted against reciprocal absolute temperature. From the slope of such a plot the enthalpy change of the process can be calculated, its size being a measure of the temperature dependence. The data in red show the effect of temperature on LDH release in the absence of xenon. The reduction of release as the temperature is reduced is expected but modest. When

12.5% xenon is present, the temperature dependence is very large and unexpected. Hypothermia therefore appears to greatly enhance the neuroprotective effects of xenon. Accordingly, the results suggest that hypothermia and xenon act synergistically as neuroprotectants.

Various modifications and variations of the described methods of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the relevant fields are intended to be within the scope of the following claims.

CLAIMS

1. Use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said medicament is for use in combination with hypothermia.

2. Use according to claim 1 wherein the xenon is admixed with a pharmaceutically acceptable diluent, excipient or carrier.

3. Use according to claim 1 or claim 2 wherein the medicament is in gaseous form.

4. Use according to claim 3 wherein the medicament is administered by inhalation.

5. Use according to any preceding claim wherein the xenon is administered in the form of a 20 to 70 % v/v xenon/air mixture.

6. Use according to claim 1 or claim 2 wherein the xenon is administered by perfusion.

7. Use according to claim 1 or claim 2 wherein the medicament is in the form of a liquid or solution.

8. Use according to claim 7 wherein the medicament is in the form of a lipid emulsion.

9. Use according to claim 7 or claim 8 wherein the medicament is in a form suitable for intravenous, neuraxial or transdermal delivery.

10. Use according to any preceding claim wherein the xenon is administered simultaneously, sequentially or separately with hypothermia.

11. Use according to claim 10 wherein the xenon is administered simultaneously with hypothermia.

12. Use according to any preceding claim wherein the hypothermia is maintained for a period of at least about 6 hours after the hypoxic-ischemic (HI) insult.

13. Use according to any one of claims 1 to 11 wherein the hypothermia is maintained for a period of from about 6 to about 24 hours after the hypoxic-ischemic (HI) insult.

14. A method of treating neonatal asphyxia in a mammal in need thereof, said method comprising:

(a) administering a therapeutically effective amount of xenon to the mammal; and

(b) subjecting the mammal to hypothermia.

15. A method according to claim 14 wherein the mammal is a human.

16. A method according to claim 14 or claim 15 wherein the xenon is administered in combination with a pharmaceutically acceptable carrier, diluent or excipient.

17. A method according to any one of claims 14 to 16 wherein the xenon is administered by inhalation.

18. A method according to claim 19 wherein the xenon is administered in the form of a 20 to 70 % v/v xenon/air mixture.

19. A method according to any one of claims 16 to 18 wherein the xenon is administered by perfusion.

20. A method according to any one of claims 16 to 18 wherein the xenon is administered in the form of a solution or emulsion.

21. A method according to claim 20 wherein the xenon is administered in the form of a lipid emulsion.

22. A method according to any one of claims 20 or 21 wherein the xenon is administered intravenously, neuraxially or transdermally.

23. A method according to any one of claims 14 to 22 wherein the xenon is administered simultaneously, sequentially or separately with hypothermia.

24. A method according to claim 23 wherein the xenon is administered simultaneously with hypothermia.

25. A method according to any one of claims 14 to 24 wherein the temperature of the mammal is maintained at a temperature of from about 32 °C to about 36 °C.

26. A method according to claim 25 wherein the temperature of the mammal is maintained at a temperature of from about 33 °C to about 35 °C.

27. A method according to any one of claims 14 to 26 wherein the hypothermia is maintained for a period of at least 6 hours after the hypoxic-ischemic (HI) insult.

28. A method according to any one of claims 14 to 26 wherein the hypothermia is maintained for a period of from about 6 to about 24 hours after the hypoxic-ischemic (HI) insult.

29. A method of treating neonatal asphyxia in a mammal in need thereof, said method comprising administering a therapeutically effective amount of xenon to the mammal in combination with hypothermia.

30. Use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said treatment comprises administering to a subject simultaneously, sequentially or separately xenon in combination with hypothermia.

31. Use of xenon, in combination with hypothermia, for the treatment of neonatal asphyxia.

ABSTRACT

USE

The present invention relates to the use of xenon in the preparation of a medicament for the treatment of neonatal asphyxia, wherein said medicament is for use in combination with hypothermia.

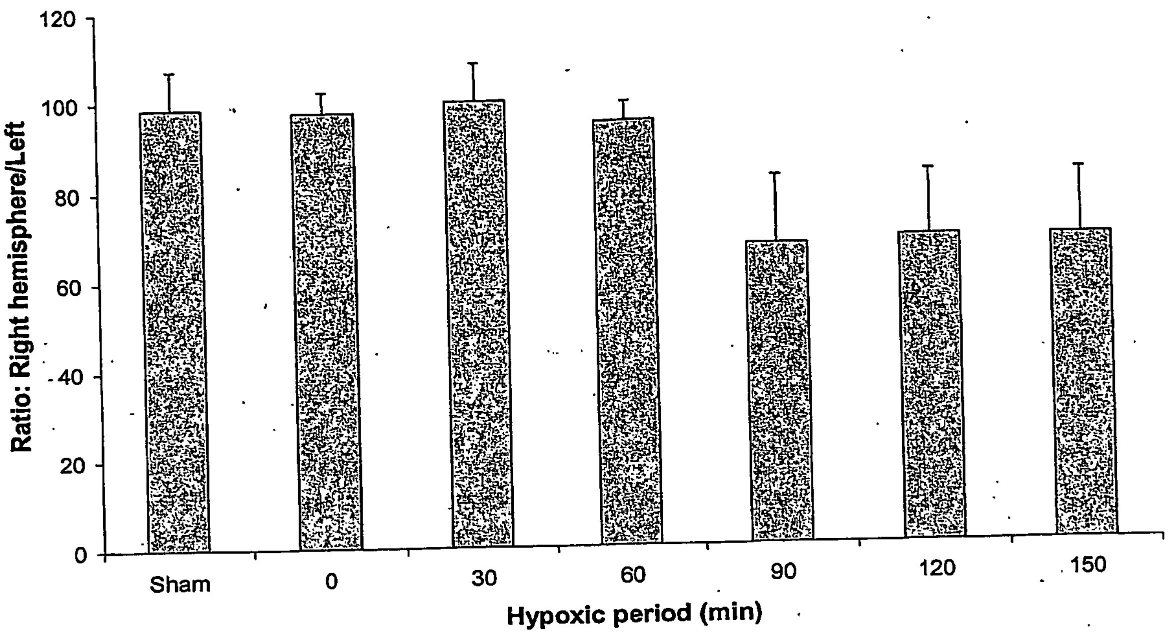

120
100
80
60
40
20
0
Ratio: Right hemisphere/Left
Sham
0
30
60
90
120
150
Hypoxic period (min)

FIGURE 1

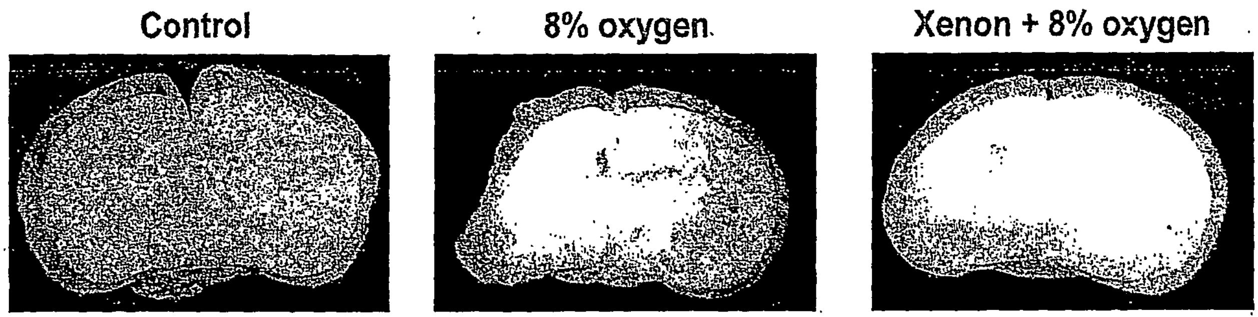


FIGURE 2

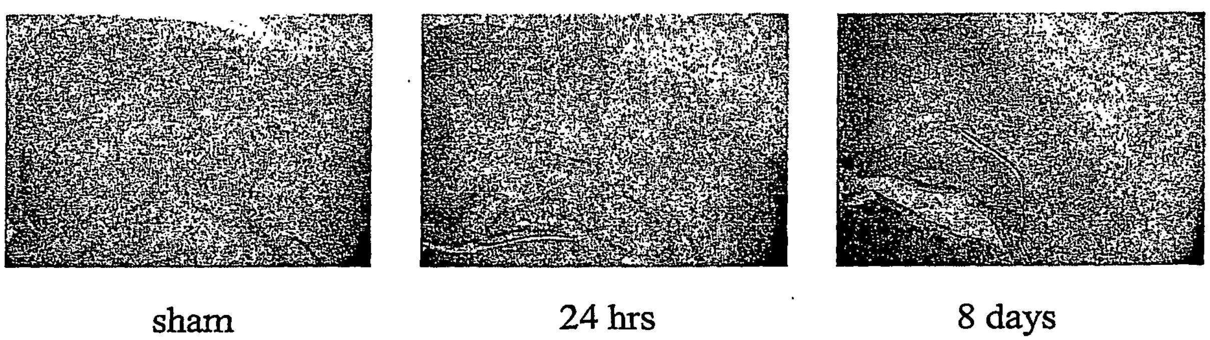


FIGURE 3

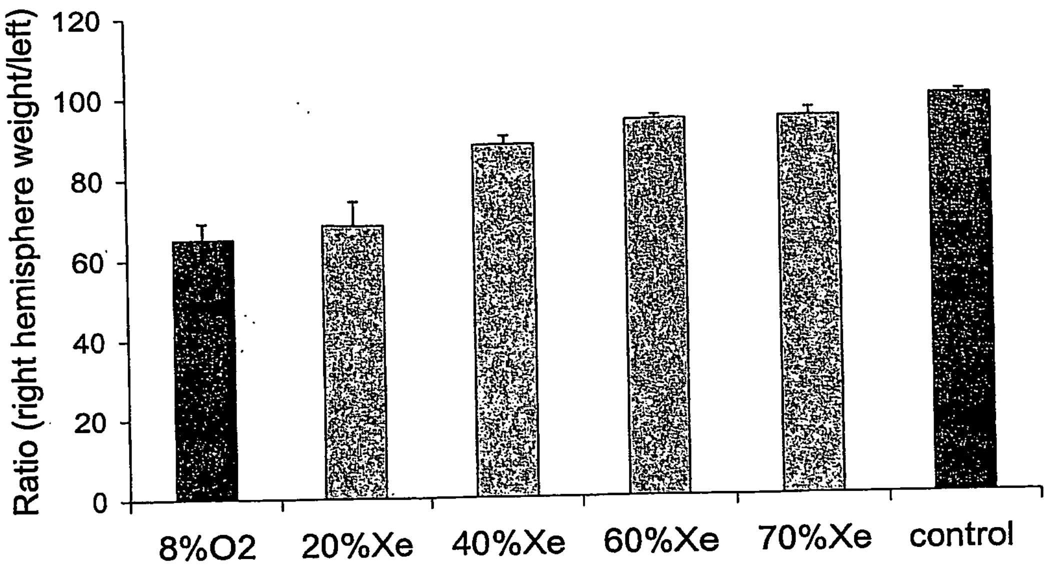

120
100
80
60
40
20
0
Ratio (right hemisphere weight/left)
8%O2
20%Xe
40%Xe
60%Xe
70%Xe
control

FIGURE 4

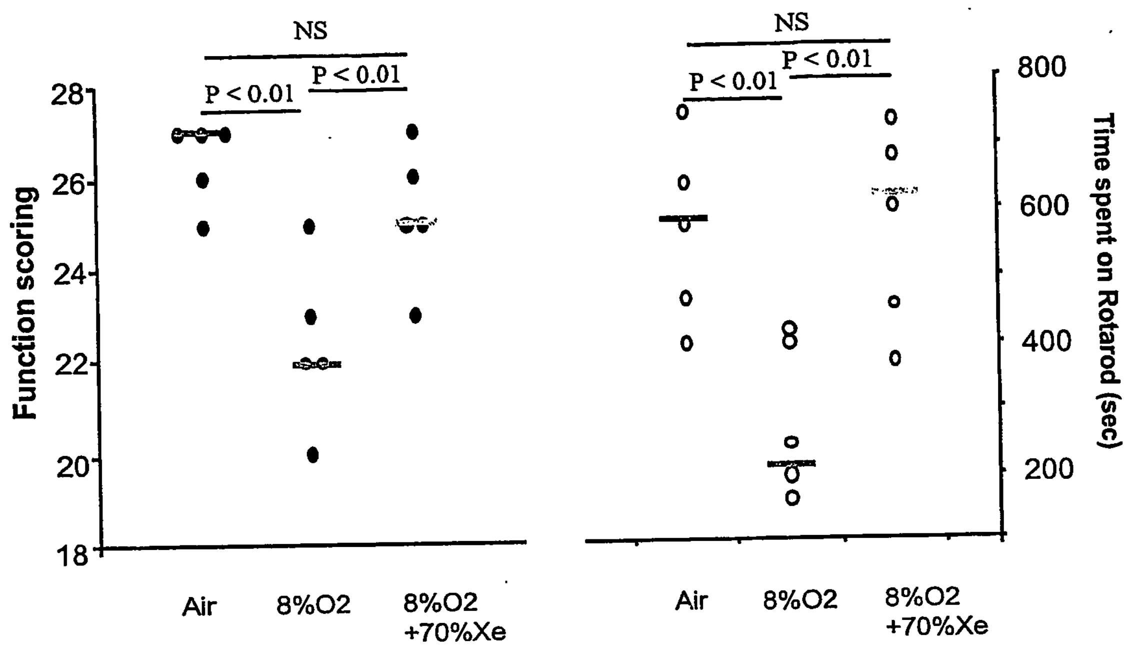

NS
P < 0.01
P < 0.01
28
26
24
22
20
18
Function scoring
Air
8%O2
8%O2
+70%Xe
NS
P < 0.01
P < 0.01
800
600
400
200
Time spent on Rotarod (sec)
Air
8%O2
8%O2
+70%Xe

FIGURE 5

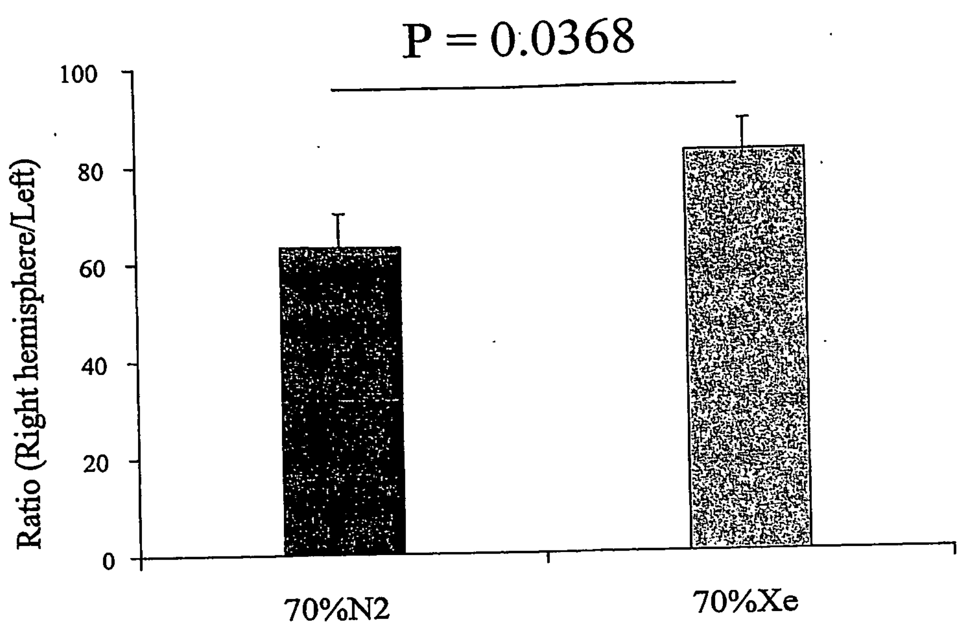

P = 0.0368
100
80
60
40
20
0
Ratio (Right hemisphere/Left)
70%N2
70%Xe

FIGURE 6

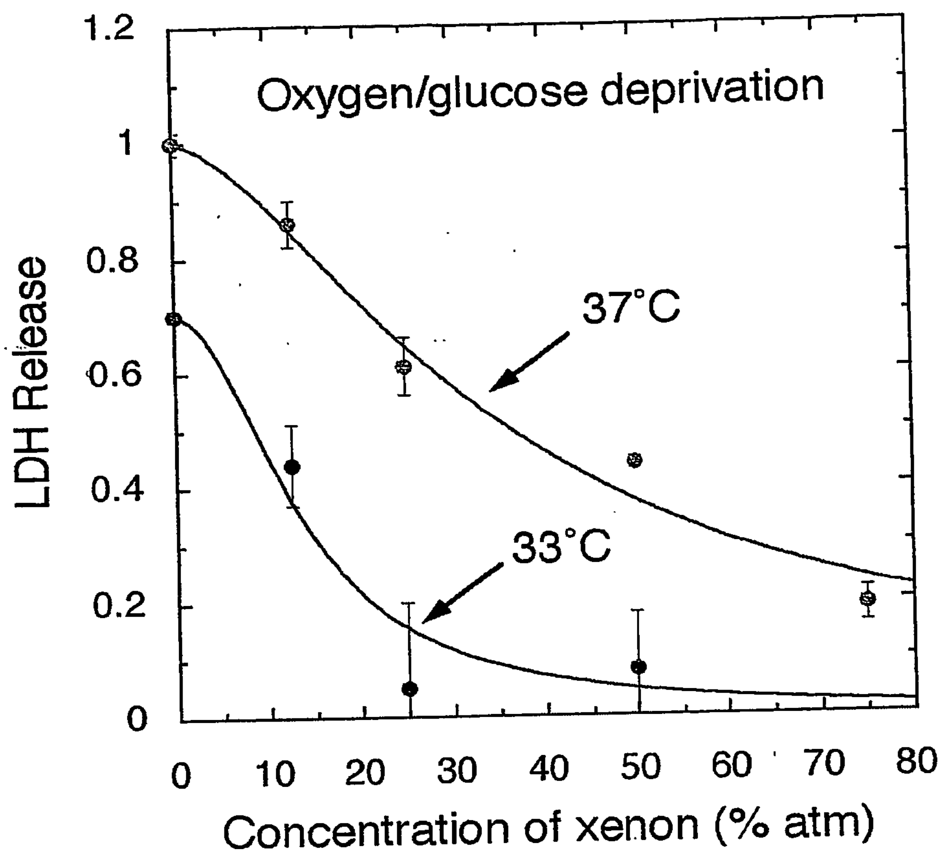
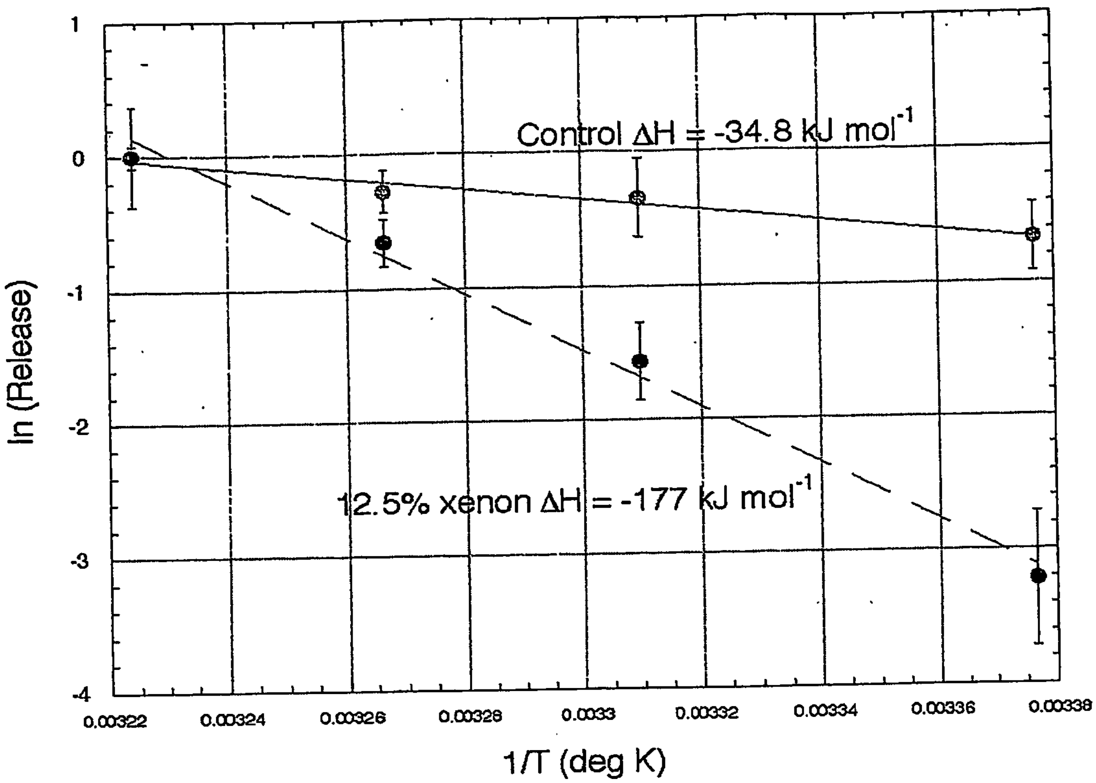

Oxygen/glucose deprivation
37°C
33°C
LDH Release
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
80
Concentration of xenon (% atm)

FIGURE 7



Control ΔH = -34.8 kJ mol-1
12.5% xenon ΔH = -177 kJ mol-1
ln (Release)
1
0
-1
-2
-3
-4
0.00322
0.00324
0.00326
0.00328
0.0033
0.00332
0.00334
0.00336
0.00338
1/T (deg K)

FIGURE 8